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Asymmetric hydrogenation of α-ethylstyrenes catalyzed by chiral ruthenium complexes†

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Abstract

A combined system of $RuCl_2[(R,R)$-Me-DuPhos$](dmf)_n$ and t-C_4H_9OK catalyzes the asymmetric hydrogenation of α-ethylstyrene derivatives. The reaction proceeds with a substrate to catalyst molar ratio of up to 2600 in 2-propanol at 8 atm and room temperature to give the chiral saturated products in 81–89% ee. © 2000 Elsevier Science Ltd. All rights reserved.

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Asymmetric hydrogenation of simple aromatic olefins has been a challenging subject since 1968, when Horner[1] reported the first trial using chiral phosphine–Rh complexes. Despite numerous efforts, currently available catalyst systems, with one notable exception,[2] are not suitable for the reaction of simple α-alkylated styrenes because of the low reactivity and/or enantioselectivity. Ru and Rh complexes possessing a chiral diphosphine ligand act as excellent precatalysts of asymmetric hydrogenation of functionalized olefins such as enamides, allylic or homoallylic alcohols, and α,β- or β,γ-unsaturated carboxylic acids.[3,4] The reaction occurs via an olefin/metal π complex which is stabilized by additional ligation of a heteroatom to the metallic center.[3–5] Asymmetric hydrogenation of α-alkylstyrenes is difficult because such highly organized chelate complexes are not accessible.[4d,6–9] Chiral Ir complexes are known to catalyze the enantioselective hydrogenation of certain tri- and tetrasubstituted aromatic olefins (S/C = 25–1000, 50 atm, 81–98% ee),[10] while the reaction of α-alkylated styrenes is unknown. The high reactivity of α-alkylstryenes is obtainable with early transition metal-[11] and lanthanide-based catalysts, and the best result was recorded in a chiral Sm-catalyzed hydrogenation of α-ethylstyrene, giving 96% ee at 1 atm and −80°C or 64% ee at 25°C (S/C = 100–1000).[2,12] We here describe a new method for activating chiral Ru complexes for the asymmetric hydrogenation of α-alkylated styrene derivatives.

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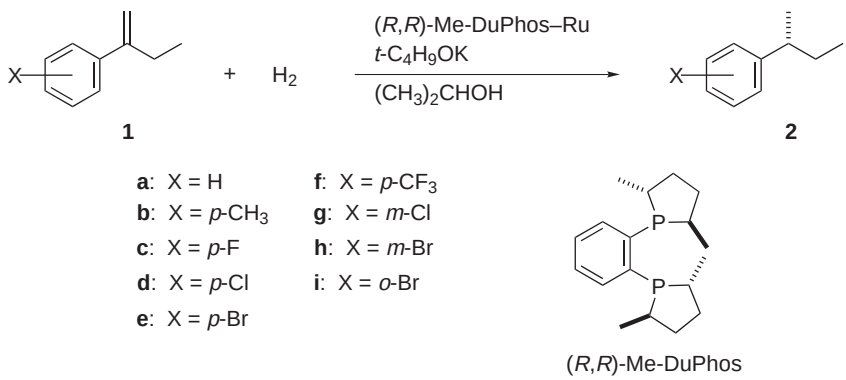
Ru complexes of type $RuCl_2$(diphosphine)$(dmf)_n$[13] have a low reactivity for the hydrogenation of styrene derivatives, but the catalytic activity is markedly enhanced by the addition of an alkaline base in 2-propanol. Thus, in the presence of $RuCl_2$[(*R*,*R*)-Me-DuPhos](dmf)$_n$[14,15] and *t*-C_4H_9OK (1:20) in 2-propanol, a series of α-ethylstyrenes **1** were smoothly hydrogenated at 8 atm and at room temperature in an enantioselective manner (Scheme 1). The reaction was performed with S/C of up to 2600 to give the chiral products (*R*)-**2** in 81 to 89% ee.[16,17] Examples of the asymmetric hydrogenation are given in Table 1. The absolute configuration of the *meta*- or *para*-halogenated products was determined after dehalogenation with a $LiAlH_4$–$CeCl_3$ mixture[18] or hydrogenolysis catalyzed by 10% Pd/C.[19] Hydrogenation of the *meta*- or *para*-substituted substrates gave the chiral 2-arylbutanes with consistently high selectivity. The highest value, 89%, was obtained with *m*-chloro-α-ethylstyrene (**1g**). The enantioselectivity was found to be relatively insensitive to the substituents. However, the *ortho*-brominated analogue **1i** gave only moderate chemical and optical yield. When the relative reactivities of the *para*-substituted olefins (independent experiments) are plotted against the σ value, a linear relationship with $\rho = 0.10$ is obtained, indicating a very low sensitivity to substituent effects. *p*-Hydroxy-α-ethylstyrene was inert to the standard conditions. A 2:1 mixture of *cis*- and *trans*-2-(*p*-bromophenyl)-2-butene was recovered without hydrogenation, suggesting that reaction of α-ethylstyrenes occurs directly without isomerization to the internal olefins. The electron-donating Me-DuPhos,[14] as the catalyst ligand, appears to greatly facilitate the reaction. The bulkier Et-DuPhos or BINAP, a fully aromatic phosphine, was not effective. Replacement of 2-propanol solvent by methanol or *t*-butyl alcohol sharply decreased the chemical and/or enantioselectivity. The presence of a strong base was crucial. Otherwise, the reactivity was significantly reduced, and the sense of enantioselection was reversed. For example, hydrogenation of **1e** without *t*-C_4H_9OK (S/C = 660, 8 atm) proceeded ca. ten times more slowly (initial rate) than in the presence of base, giving the *S*-configurated product in 21% ee.



Scheme 1.

It is well known that the treatment of Ru halides with an alkaline base in 2-propanol generates Ru hydride species that are capable of catalyzing the transfer hydrogenation of carbonyl compounds.[4d,20] However, the present system does not promote saturation of styrene derivatives without H_2. Both H_2 and 2-propanol are necessary for high reactivity. The reaction of **1e** using D_2 and $(CH_3)_2CHOH$ (S/C = 500, 10 atm, 25°C, 16 h) gave the corresponding vicinal dideuterio compound selectively (ca. 90% at α position and >95% at β position by ^1H NMR analysis, 83% ee), confirming the net hydrogenation.

Table 1
Asymmetric hydrogenation of α-ethylstyrenes catalyzed by (*R*,*R*)-Me-DuPhos–Ru complex[a]

Olefin	S/C[b]	% Conv.[c]	Product **2**		
			% Yield[d]	% Ee[e]	Config.[f]
1a	200	100	92	86[g]	*R*
1b	330	87	83[h]	87	*R*
1c	660	97	83	82[i]	*R*[j]
1d	1380	94	88[h]	85	*R*[j]
1e	660	100	89	83[k]	*R*[j]
1f	2620	99.5	93	81[l]	*R*
1g	520	87	81[h]	89	*R*[j]
1h	520	100[m]	89[m]	86[n]	*R*[j]
1i	390	33	–[o]	69	*R*[j]

[a] Unless otherwise stated, reactions were conducted at 8 atm of H_2 and 18–25°C for 16 h using a 2.0–2.5 M solution of **1** (95–99% pure) in 2-propanol containing $RuCl_2$[(*R*,*R*)-Me-DuPhos](dmf)$_n$ and *t*-C_4H_9OK (1:20 molar ratio).
[b] Substrate:catalyst molar ratio.
[c] GC analysis.
[d] Isolated yield after bulb-to-bulb distillation.
[e] Chiral GC analysis (β-cyclodextrin phase).
[f] Determined by the sign of rotation of the pure or substrate-contaminated product.
[g] Determined by the rotation value, $[\alpha]_D^{22}$ −24.5° (*c* 0.53, 95% C_2H_5OH); lit. Lardicci, L.; Menicagli, R.; Salvadpri, P. *Gazz. Chim. Ital.* **1968**, *98*, 738–759, $[\alpha]_D^{25}$ +28.4° (*c* 1.00, 95% C_2H_5OH) for (*S*)-**2a**.
[h] Contaminated with ca. 5% of **1**.
[i] $[\alpha]_D^{20}$ −22.8° (*c* 2.5 C_2H_5OH).
[j] Determined after conversion to **2a**.
[k] $[\alpha]_D^{22}$ −15.1° (*c* 2.5, C_2H_5OH).
[l] See Ref. 16.
[m] Formation of 1% *cis*- and *trans*-2-(*m*-bromophenyl)-2-butene was observed.
[n] $[\alpha]_D^{17}$ −22.1° (*c* 1.0, 95% C_2H_5OH).
[o] A 67:33 mixture of **1i** and **2i**.

The present chiral catalyst system hydrogenates certain aromatic olefins under mild reaction conditions and with respectable enantioselectivity. The reactivity and chiral efficiency are better than those accessible with the conventional Ru or Rh catalysts.[4,6]

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16. $RuCl_2$[(*R*,*R*)-Me-DuPhos](dmf)$_n$ (1.5 mg, 0.0024 mmol, calculated as n = 2) was placed in a 100-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, and the air in this apparatus was replaced with argon. 2-Propanol (1.2 mL), **1f** (1.26 g, 6.29 mmol), and a 1.0 M t-C_4H_9OK solution in t-butyl alcohol (47 μL, 0.047 mmol) were added to the autoclave, and the mixture was degassed. Hydrogen was introduced into the autoclave at a pressure of 8 atm. The reaction mixture was vigorously stirred at 20°C for 16 h. The conversion determined by GC was 99.5%. GC [Chirasil-DEX CB, df = 0.25 mm, 0.32 mm i.d.×25 m, CHROMPACK; carrier gas, helium (26 kPa); column temp., 89°C; retention time (t_R) of (*R*)-**2f**, 34.0 min (90.0%); t_R of *S* isomer 32.9 min (9.5%); t_R of **1f**, 42.9 min (0.5%)]. After the reaction, the solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation to give (*R*)-**2f** (1.18 g, 93% yield, 81% ee). No starting

substrate was detected. $[\alpha]_D^{22}$ −17.0° (*c* 3.0, C_6H_6), lit. $[\alpha]_D^{22}$ +19.6° (*c* 5, C_6H_6), 94% ee (*S*), Capillon, J.; Guetté, J. P. *Tetrahedron* **1979**, *35*, 1807–1815.

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